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The Clinical Impact of Routine Angiographic Follow-Up in Randomized Trials of Drug-Eluting Stents

A Critical Assessment of "Oculostenotic" Reintervention in Patients With Intermediate Lesions

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Objectives The aim of this study was to study the long-term clinical effects of routine angiographic follow-up and related reintervention after drug-eluting stenting.

Background Prior stent trials have shown that protocol-mandated angiographic follow-up increases repeat interventions compared with clinical follow-up alone. The long-term clinical impact of this practice is unknown.

Methods Long-term outcomes of patients assigned to routine angiographic follow-up in 3 large-scale TAXUS (Boston Scientific, Natick, Massachusetts) trials were compared with patients assigned to clinical follow-up alone, in a propensity score-adjusted patient-level meta-analysis. Outcomes were also compared in patients with treated versus untreated nonischemic intermediate lesions (quantitative angiographic stenosis between ≥40% and <70%) detected at angiographic follow-up.

Results Target lesion revascularization (TLR) rates at 5 years were significantly higher in the angiographic compared with clinical follow-up cohort (18.3% vs. 11.1%, $p < 0.001$). This was due to more frequent treatment of intermediate lesions, but there was no associated reduction in rates of cardiac death or myocardial infarction (8.9% vs. 8.8%, $p = 0.93$). Of patients with nonischemic intermediate lesions, 17% who were not revascularized at the time of angiographic follow-up had a subsequent TLR, whereas 7% of patients who had TLR at this follow-up angiogram required additional revascularization during long-term follow-up.

Conclusions A strategy of routine angiographic follow-up increases oculostenotic revascularization of nonischemic intermediate lesions without affecting subsequent rates of cardiac death or myocardial infarction, and TLR was not required in 83% of those lesions. A conservative approach, in which repeat angiography is limited to patients with recurrent ischemia or progressive symptoms, minimizes repeat revascularization of nonischemic intermediate lesions and optimizes long-term event-free survival after drug-eluting stent implantation. (J Am Coll Cardiol Intv 2010;3:403–11) © 2010 by the American College of Cardiology Foundation

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Percutaneous coronary intervention (PCI) is the revascularization strategy of choice for many patients with coronary heart disease. Outside of clinical research trials, current U.S. and European guidelines recommend clinical follow-up after PCI, with angiography reserved to evaluate patients who have recurrent symptoms or objective evidence of myocardial ischemia (1,2). This is based on the knowledge that ischemic symptoms correlate with an increased risk of adverse clinical outcomes (3,4) and that revascularization of the ischemic culprit lesions can improve both functional status and subsequent patient outcome (4–6). In contrast, coronary lesions that do not produce ischemia typically fail to benefit from revascularization compared with continued optimal medical therapy alone (7–9). Nonetheless, routine 6-month angiography is still performed in selected centers in an effort to identify angiographic significant stenoses that have not resulted in ischemic signs or symptoms (10), despite the added cost and small associated procedural risk (11–14).

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CEC = clinical events committee
DES = drug-eluting stent(s)
DN = de novo
DS = diameter stenosis
MI = myocardial infarction
PCI = percutaneous coronary intervention
PES = paclitaxel-eluting stent(s)
QCA = quantitative coronary angiography
TLR = target lesion revascularization
TVR = target vessel revascularization
WH = workhorse

Numerous trials of balloon angioplasty, bare-metal stents (BMS), and drug-eluting stents (DES) have shown that patients who undergo mandatory angiographic follow-up tend to receive significantly more repeat revascularization procedures than those having clinical follow-up alone (10,15–18), via a phenomenon known as the "oculostenotic" reflex (19,20). It is unknown how routine angiographic follow-up affects long-term clinical outcomes—whether the associated increase in repeat revascularization provides any clinical benefit by reducing the subsequent incidence of myocardial infarction (MI) or mortality during longer-term observation (10,18,21) or is perhaps even harmful.

We therefore performed a patient-level meta-analysis on the combined TAXUS IV and V (de novo [DN]) and ATLAS (Workhorse [WH]) trials to compare the clinical outcomes of patients assigned to routine angiographic follow-up with those assigned to clinical follow-up alone. We also performed a landmark analysis of patients with angiographically intermediate, nonischemic lesions to assess any long-term clinical benefit among those who were or were not revascularized at the time of angiographic follow-up.

Methods

Study population. The patient-level databases of the prospective, randomized, double-blind TAXUS IV (n = 1,314; 5-year follow-up) (22,23) and TAXUS V-DN (n = 1,156; 4-year follow-up) (24) trials for the TAXUS Express stent were pooled with the TAXUS Liberté stent arm of the historically controlled TAXUS ATLAS-WH (n = 871, 3-year follow-up) trial (25), in a patient-level meta-analysis (total n = 3,341). These studies comprise the pivotal trials for the TAXUS Express and TAXUS Liberté paclitaxel-eluting stents (PES) (Boston Scientific, Natick, Massachusetts). Angiographic follow-up was prespecified in a subset of TAXUS IV and ATLAS-WH patients and in all TAXUS V-DN patients (total n = 2,431); clinical-only follow-up was assigned in the other 910 patients.

End points and definitions. In-segment percentage diameter stenosis (DS) was defined as percentage stenosis within the analysis segment that included the 5-mm proximal to 5-mm distal margins of the stent. Adverse cardiac events (cardiac death or MI, target lesion revascularization [TLR], target vessel revascularization [TVR], nontarget lesion TVR, and Academic Research Consortium definite/probable stent thrombosis [26]) were adjudicated by independent clinical events committees (CECs) during the course of each trial. The TLR was adjudicated as ischemia-driven (clinically driven) if the target lesion was >70% DS by quantitative coronary angiography (QCA) or for DS between ≥50% and ≤70% if the CEC determined there was objective evidence of ischemia. Site-reported TLR (i.e., nonclinically driven TLR, not confirmed as ischemic-driven by the CEC) was also analyzed.

For the landmark analysis, any revascularization occurring <14 days after routine follow-up angiography was excluded as a long-term end point to avoid including staged revascularization procedures as long-term events. Other end points were included from the date of angiographic follow-up.

Statistical analysis. Analysis of the intent-to-treat sample was conducted with SAS System Software, version 8.0 or higher (SAS Institute, Cary, North Carolina). Categorical variables were compared by chi-square or Fisher exact test. Continuous variables were described as mean ± SD and were compared with analysis of variance. Time-to-event data were reported and displayed as Kaplan-Meier estimates with comparisons between groups by the log-rank test. The Cox proportional hazard model was used to assess long-term clinical outcomes.

To minimize bias due to baseline differences between the routine angiographic (which included the more complex TAXUS V patients) and clinical follow-up groups, Greedy 1:1 matching was performed with a propensity score generated by a logistic regression model. Covariates for this model were selected if they differed significantly between the 2 groups or were clinically important; colinearity and results of the goodness-of-fit test were also considered in selection. The covariates included binary variables (sex, prior coronary artery bypass graft surgery, diabetes, hypertension, hyperlipidemia, smoking, history of coronary artery disease, left anterior descending artery location, tortuosity, multiple

stents, and American College of Cardiology/American Heart Association B2/C lesions) and continuous variables (age, baseline reference vessel diameter [QCA], and lesion length [QCA]). A total of 13 patients were unable to be matched, due to missing baseline values.

Annualized hazard rates were calculated for cardiac death or MI, TVR, TLR, and nontarget lesion TVR (for 0 to 1 year and >1 to 5 years) with the person-time method and were expressed as the event rate/100 patient-years (equivalent to event percentage/patient/year). To determine the impact of stenosis on TLR in the 2 follow-up cohorts, stenosis was divided into 3 categories: mild (<40% DS), intermediate (≥40% to <70%), and severe (≥70%). A landmark analysis was performed on patients who were event-free up until the 9-month follow-up.

Results

Patient characteristics. Patients were pooled from the TAXUS IV, V-DN, and ATLAS-WH trials (n = 3,341); 72% had been randomly assigned to receive mandated angiographic follow-up (BMS n = 936; PES n = 1,495), whereas 28% were assigned to clinical follow-up only (BMS n = 295; PES n = 615). Groups of routine angiographic and clinical-only follow-up patients were matched on the basis of propensity score, to minimize any imbalances in their baseline characteristics (n = 897 patients from each follow-up group; Table 1).

Effect of routine angiographic follow-up on clinical events. As shown in Figure 1, the rates of TLR were similar in the angiographic and clinical follow-up cohorts (Fig. 1A) until 9-month protocol-mandated angiography, at which time the rate of overall TLR increased abruptly in the angiographic group. After the close of the angiographic follow-up window, the rates of ischemic TLR in the 2 cohorts again paralleled each other. Similar results were found when PES-treated patients were analyzed separately (Fig. 1C). However, in the BMS-treated patient cohort, there were more early clinically driven TLRs than in the PES-treated cohort. This might have resulted in there being no statistically significant difference between the clinical-only and angiographic follow-up groups in the BMS-treated cohort (Fig. 1B). Due to lower rates of TLR in PES (angiographic 15.9% vs. clinical-only 7.4%, p < 0.001) compared with BMS (23.6% angiographic vs. 18.9% clinical-only, p = 0.17), angiographic follow-up had greater relative impact on the overall TLR rates in PES-treated patients (odds ratio

Table 1. Clinical and Angiographic Characteristics in Unadjusted and Propensity-Matched Cohorts

	Unadjusted Patient Population			Propensity-Matched Patient Population		
	Follow-Up*			Follow-Up*		
	Clinical (n = 910)	Angiographic (n = 2,431)	p Value	Clinical (n = 897)	Angiographic (n = 897)	p Value
Age (yrs)	62.1 ± 11.0	62.6 ± 10.9	0.30	62.1 ± 11.0	61.9 ± 11.1	0.64
Female	27.6	30.2	0.13	27.4	26.8	0.79
Prior PCI	32.0	32.0	0.97	32.0	30.9	0.65
Prior CABG	6.8	10.5	<0.001	6.9	6.9	>0.99
Unstable angina	31.5	32.8	0.48	31.4	31.1	0.92
Stable angina	55.7	55.7	0.99	56.0	58.0	0.42
Diabetes mellitus	22.9	28.2	0.002	22.7	22.4	0.91
Hypertension	69.2	73.2	0.02	69.4	69.1	0.92
Hyperlipidemia	69.9	71.2	0.44	69.9	70.9	0.68
Smoking	24.9	23.7	0.51	22.2	23.9	0.43
History of coronary artery disease	54.6	58.4	0.049	54.7	56.6	0.45
Renal disease	3.4	4.5	0.18	3.3	4.4	0.32
Baseline lesion characteristics						
RVD (QCA), (mm)	2.7 ± 0.5	2.7 ± 0.5	0.91	2.7 ± 0.5	2.8 ± 0.5	0.22
Lesion length (QCA), (mm)	12.8 ± 5.6	15.9 ± 8.2	<0.001	12.9 ± 5.6	12.9 ± 5.9	0.83
QCA DS	67.0 ± 11.0	67.9 ± 11.5	0.04	66.9 ± 10.9	67.1 ± 11.4	0.72
Multiple stents	6.9	19.7	<0.001	5.2	5.2	>0.99
Ejection fraction	55.5 ± 9.9	55.3 ± 10.0	0.72	55.5 ± 10.0	55.6 ± 9.6	0.87
AHA/ACC type B2/C lesions	56.0	72.0	<0.01	56.1	57.0	0.74

Values are mean ± SD or %. The p value for continuous data from analysis of variance. The p value for categorical data from chi-square test. *Includes patients receiving either bare-metal or paclitaxel-eluting stent.

ACC/AHA = American College of Cardiology/American Heart Association; DS = diameter stenosis; CABG = coronary artery bypass graft surgery; PCI = percutaneous coronary intervention; QCA = quantitative coronary angiography; RVD = reference vessel diameter.

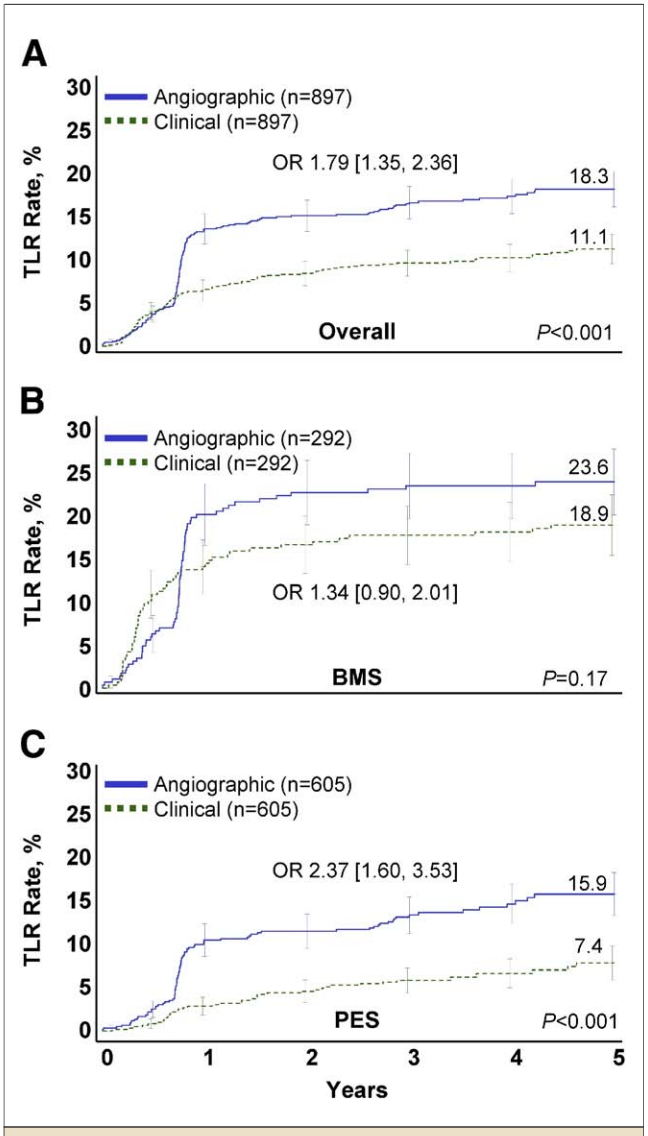

Figure 1. Cumulative Rate of TLR in Patients With Angiographic or Clinical-Only Follow-Up

Target lesion revascularization (TLR) is increased in patients with routine angiographic compared with clinical-only follow-up, for the propensity-matched complete group **(A)** and the bare-metal stent (BMS) **(B)** and paclitaxel-eluting stent (PES) **(C)** cohorts. OR = odds ratio.

[95% confidence interval]: PES 2.37 [1.60 to 3.53] vs. BMS 1.34 [0.90 to 2.01], p = 0.048).

The higher rates of overall TLR in the routine angiography cohort were not associated with any significant difference in the subsequent combined end point of cardiac death or MI in the overall patient population or in either BMS- or PES-treated patients (Figs. 2A to 2C). Similar results were found when outcomes were analyzed as annualized hazard rates (Table 2). Other than the previously noted significant difference in TLR and TVR between 9 months and 1 year, there was no significant increase or decrease in either measure of repeat revascularization from 1 through 5 years. A borderline increase in nontarget lesion TVR at 1 year was also present, with no significant differences in the rate of cardiac death or MI or in Academic Research Consortium definite/probable stent thrombosis between the 2 follow-up strategies during the first or subsequent years.

Evidence for differential oculostenotic treatment of intermediate lesions. The influence of the follow-up strategy on the relationship between baseline %DS and overall TLR between 90 and 300 days is shown for the unadjusted and propensity-matched patient populations (Fig. 3). Few patients with mild lesions (%DS <40%) had repeat revascu-

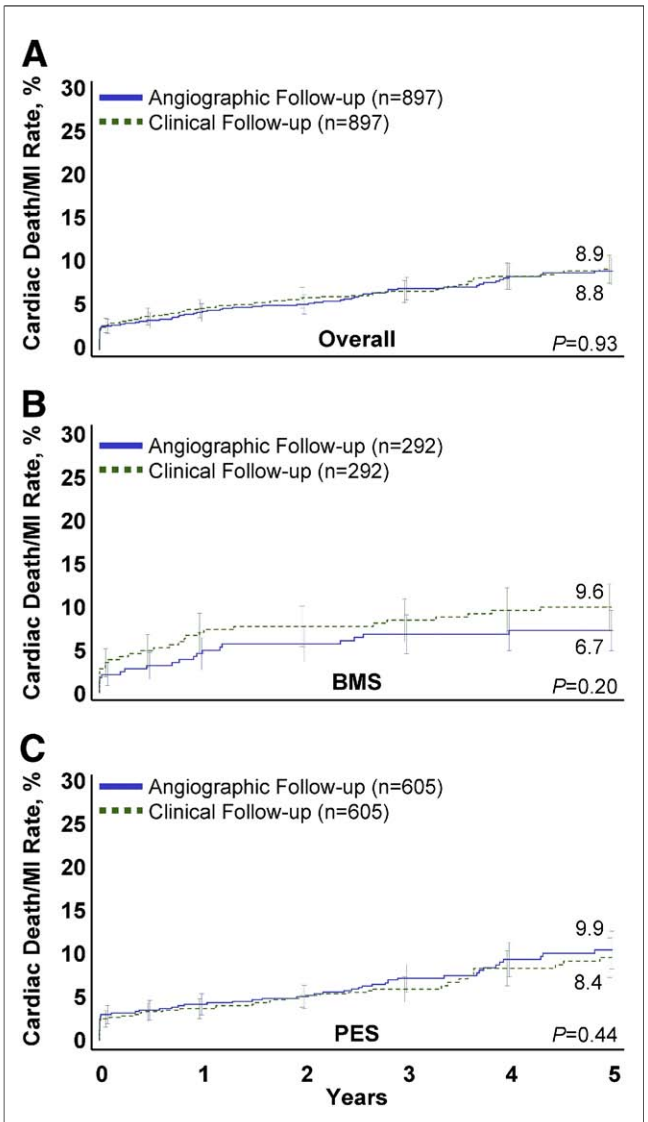

Figure 2. Cumulative Rate of Cardiac Death or MI in Patients With Angiographic or Clinical-Only Follow-Up

There was no statistically significant difference in rate of cardiac death or myocardial infarction (MI) between the propensity-matched routine angiographic and clinical-only follow-up cohorts for the complete group **(A)** or the BMS **(B)** and PES **(C)** cohorts. Abbreviations as in Figure 1.

Table 2. Annualized Hazard Rates for Propensity-Matched Patients Assigned to Clinical Versus Angiographic Follow-Up

	0–1 Year				>1–5 Years			
	Annualized Hazard Rate, % (95% CI)				Annualized Hazard Rate, % (95% CI)			
	Clinical Follow-Up	Angiographic Follow-Up	Hazard Ratio (95% CI)	p Value	Clinical Follow-Up	Angiographic Follow-Up	Hazard Ratio (95% CI)	p Value
Overall	n = 897	n = 897			n = 873	n = 862		
Cardiac death or MI	4.9 (3.4–6.4)	4.4 (3.0–5.9)	0.9 (0.6–1.4)	0.66	1.2 (0.8–1.6)	1.5 (1.0–2.0)	1.3 (0.8–2.0)	0.36
TVR	8.5 (6.5–10.5)	18.3 (15.4–21.2)	2.2 (1.6–2.9)	<0.001	3.1 (2.4–3.8)	3.5 (2.7–4.2)	1.1 (0.8–1.5)	0.50
TLR	6.7 (5.0–8.4)	14.2 (11.7–16.8)	2.1 (1.6–2.9)	<0.001	1.5 (1.0–2.0)	2.0 (1.4–2.5)	1.3 (0.9–2.0)	0.23
Non-TL TVR	2.7 (1.6–3.8)	4.6 (3.2–6.1)	1.7 (1.0–2.8)	0.04	1.8 (1.3–2.3)	1.8 (1.2–2.3)	1.0 (0.6–1.5)	0.88
BMS	n = 292	n = 292			n = 279	n = 283		
Cardiac death or MI	7.3 (4.1–10.5)	4.7 (2.1–7.2)	0.6 (0.3–1.3)	0.21	0.9 (0.3–1.4)	1.0 (0.4–1.7)	1.1 (0.4–2.8)	0.86
TVR	16.9 (11.9–21.9)	25.3 (19.2–31.4)	1.5 (1.0–2.2)	0.04	3.7 (2.5–4.9)	2.7 (1.6–3.8)	0.7 (0.4–1.2)	0.24
TLR	15.3 (10.6–20.0)	21.5 (15.9–27.1)	1.4 (0.9–2.1)	0.10	1.7 (0.9–2.5)	1.5 (0.7–2.3)	0.9 (0.4–1.8)	0.69
Non-TL TVR	3.5 (1.3–5.7)	4.6 (2.1–7.1)	1.3 (0.6–3.0)	0.52	2.2 (1.3–3.1)	1.2 (0.5–2.0)	0.6 (0.3–1.2)	0.14
PES	n = 605	n = 605			n = 590	n = 583		
Cardiac death or MI	3.8 (2.2–5.4)	4.3 (2.6–6.0)	1.1 (0.6–2.0)	0.65	1.4 (0.8–2.0)	1.8 (1.1–2.5)	1.3 (0.7–2.2)	0.40
TVR	4.8 (3.0–6.5)	15.1 (11.9–18.3)	3.2 (2.1–4.9)	<0.001	2.8 (1.9–3.6)	4.0 (2.9–5.0)	1.4 (1.0–2.1)	0.09
TLR	2.9 (1.5–4.2)	10.8 (8.1–13.5)	3.8 (2.2–6.5)	<0.001	1.4 (0.8–2.0)	2.2 (1.5–3.0)	1.6 (0.9–2.8)	0.08
Non-TL TVR	2.4 (1.1–3.6)	4.6 (2.9–6.4)	2.0 (1.0–3.8)	0.04	1.5 (0.9–2.2)	2.1 (1.4–2.8)	1.3 (0.8–2.2)	0.35

Rate/100 patient-years.

BMS = bare-metal stent(s); CI = confidence interval; MI = myocardial infarction; Non-TL TVR = non–target lesion target vessel revascularization; PES = paclitaxel-eluting stent(s); TLR = target lesion revascularization; TVR = target vessel revascularization.

larization, regardless of the type of follow-up. In contrast, the routine angiography group had a much higher rate of revascularization for intermediate lesions (%DS ≥40% and <70% by QCA). For severe lesions (≥70% DS by QCA), the rates of TLR were again largely similar in patients with angiographic versus only clinical follow-up. Thus in the propensity-matched patient population, the 5.7% overall difference in absolute TLR rates between the 2 follow-up groups (angiographic 10.4% vs. clinical 4.7%) was due mostly (65%) to revascularization of lesions in the intermediate (≥40 to 70% DS) range, with the remaining 35% of the difference found in lesions at the lower end of severe (≥70% DS) stenosis.

Outcomes in patients with revascularized intermediate lesions. Among 316 patients in whom intermediate lesions were found on the 9-month protocol-mandated angiogram, 63 (19.9%) were adjudicated by the CEC to have had ischemia-driven TLR, and 45 (14.2%) were adjudicated to have had angiographically driven TLR without evidence of ischemia. An additional 208 patients with intermediate lesions were not treated at the time of 9-month angiographic follow-up; a comparison group (n = 1,142) of nontreated patients with mild lesions (<40% DS by QCA) was also identified.

As shown in Table 3, the long-term rate of cardiac death or MI was higher in the intermediate lesion patients, judged to have ischemia-driven repeat revascularization, than in those with angiographically driven TLR or no TLR (11.5%, 2.2%, and 5.2%, respectively). Similar results were found in each treatment arm (BMS or PES). Although the difference is not statistically significant, due to the small sample size, the ischemia-driven group had more diabetic patients (34.9% [22 of 63]) than either the angiographically driven (22.2% [10 of 45]) or untreated (23.1% [48 of 208]) groups. Also, the mean %DS in the ischemia-driven group (61.52 ± 5.23) was higher than that of the angiographically driven (55.73 ± 6.68) and untreated (50.12 ± 7.97) patient groups. These findings might provide an explanation for the apparent increase in cardiac death and MI in the ischemia-driven, intermediate lesion group.

The untreated intermediate lesion group tended to have more subsequent TLRs than in the group with nonischemic angiographically driven TLR (17.0% and 7.0%, respectively, p = 0.08) (Fig. 4). Accordingly, 83% of patients with intermediate lesions and no clinical ischemia did not require TLR during the follow-up period. In this regard, the numerical increase in the long-term rates of subsequent TLR of intermediate lesions was not significantly different for the PES group (angiography driven 10.0% vs. untreated 15.7%, p = 0.53) or the BMS group (4.0% vs. 17.9%, p = 0.08).

Discussion

The results of this study confirm that patients who are assigned to routine angiographic follow-up in clinical studies of DES undergo more TLR than patients assigned to clinical follow-up alone but have similar rates of subsequent

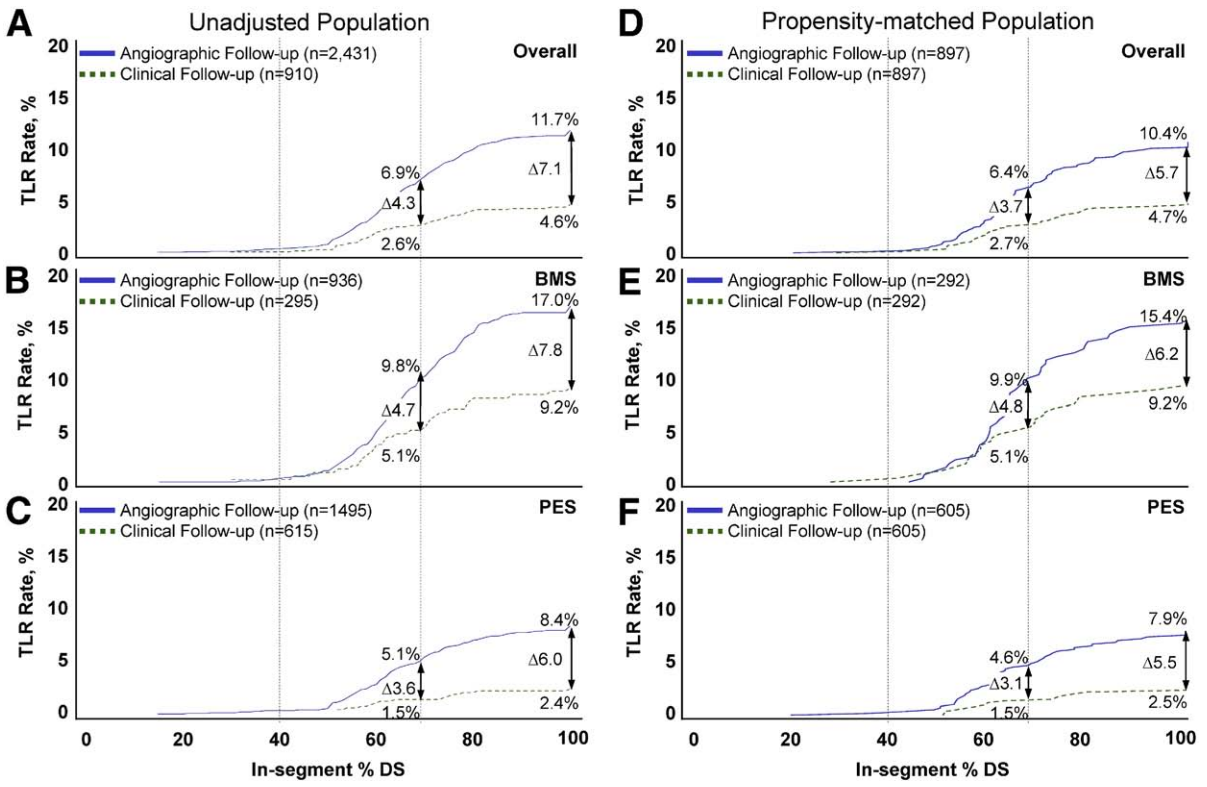

Figure 3. The TLR Rate Between 90 and 300 Days After Stent Implantation as a Function of %DS at Baseline

The largest difference in TLR rates between the follow-up groups was found in patients with intermediate lesions (≥40% to <70% diameter stenosis [DS]) in both the unadjusted and propensity-matched cohorts. Abbreviations as in Figure 1.

death or MI during long-term follow-up. Although the severity of angiographic restenosis was correlated with the likelihood of TLR, it was clear that the main effect of routine angiographic follow-up was to increase the likelihood that a patient with an intermediate restenosis (≥40 to <70% DS by QCA) but no objective evidence of ischemia would undergo repeat revascularization via the so-called oculostenotic reflex. This is particularly important, because only the minority (22%) of patients with angiographic restenosis has severe (DS >70%) stenosis most clearly associated with demonstrable myocardial ischemia (21). In addition, such intermediate lesions tend to regress over time (2 to 5 years) and generally have a favorable clinical outcome with medical therapy alone (27–29).

Table 3. Long-Term Outcomes in Patients With Treated Versus Untreated Intermediate Lesions at Follow-Up Angiography

	Intermediate Lesions*				p Value	
	Treated					
	Ischemia-Driven† (n = 63)	Angiography-Driven† (n = 45)	Untreated (n = 208)	Untreated Mild Lesions* (n = 1,142)	Angiography-Driven vs. Untreated	Untreated Intermediate vs. Mild Lesions
Death	10.1	0.0	4.9	5.9	0.13	0.68
Cardiac death	3.3	0.0	3.0	2.0	0.25	0.31
MI	8.5	2.2	2.7	1.9	0.92	0.53
Cardiac death or MI	11.5	2.2	5.2	2.6	0.43	0.26
ST‡	0.0	0.0	0.6	0.9	0.50	0.89

Values are %. Kaplan-Meier event rates at 5 years do not include staged revascularization procedures; patients were event-free until routine follow-up angiographic visit at 9-months. *Mild lesions (<40% DS); intermediate lesions (≥40 to <70% DS). †Ischemia-driven = clinical events committee-adjudicated TLR; angiography-driven = site-reported TLR. ‡Academic Research Consortium definite/probable stent thrombosis (ST). Abbreviations as in Table 2.

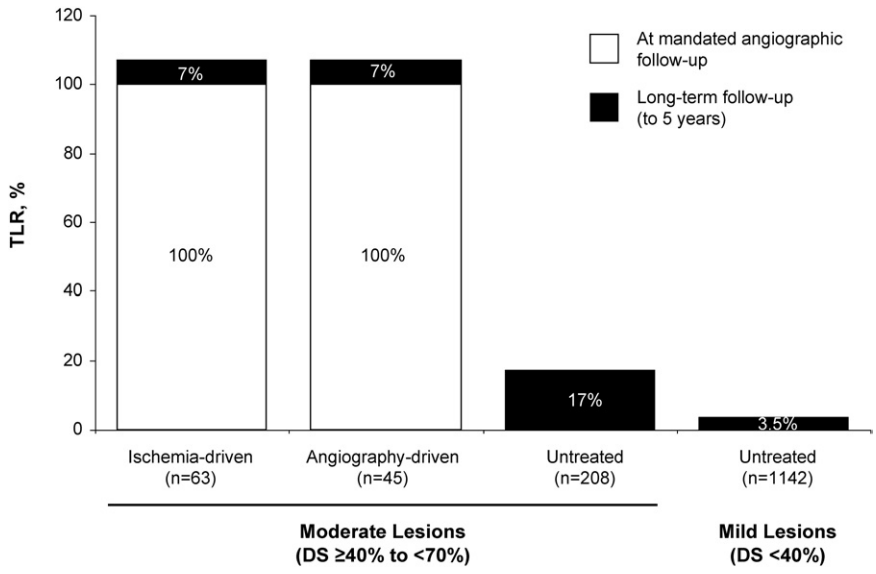

Figure 4. Rates of Subsequent TLR in Patients Who Were Treated Versus Untreated at the Time of Follow-Up Angiography

The untreated, intermediate lesion group tended to have more subsequent TLR. Abbreviations as in Figures 1 and 3.

The effect of routine follow-up angiography on increasing repeat revascularization has been documented in previous studies (15,16,30). However, the current study is unique in demonstrating that increased oculostenotic revascularization after routine follow-up angiography involved mostly the treatment of intermediate lesions. Subsequent cardiac death or MI through 5 years of follow-up was not reduced in this group compared with clinical follow-up alone with limited ischemia-driven repeat revascularization. Although patients with preemptively treated intermediate lesions after mandated angiographic follow-up did tend to have a slightly lower rate of additional TLR than those who were untreated (7% and 17%, respectively, $p = 0.08$), 83% of untreated patients avoided an additional revascularization. In contrast, all of the retreated patients had at least 1 (and some a second) repeat revascularization. There was no evidence that this increase in preemptive treatment of intermediate lesions reduced the rate of subsequent cardiac death or MI in patients undergoing routine angiographic follow-up. Although small routine angiographic follow-up cohorts might be ethically justified in trials of new stents (given the scientific information provided), such procedures should be deferred until after measurement of the primary end point to avoid interfering with the assessment of clinical efficacy or clustered in a separate angiographic cohort from which the clinical end point is determined.

These findings in patients with intermediate nonischemic lesions do not alter the recommendation that patients with recurrent symptoms or evidence of myocardial ischemia after PCI still undergo repeat clinically indicated angiography and intervention on significant restenosis or progressive disease outside the stented segment, a strategy that would be expected to improve quality of life and subsequent event-free survival (31). Despite the nonstatistically significant differences, it is interesting to note that the clinical-only follow-up group in the BMS cohort had numerically higher rates of cardiac death and MI compared with the angiographic follow-up group. The clinical-only follow-up group might have included some concealed restenosis, which parallels a previously published report where restenosis was associated with increased mortality in a BMS population (32). In contrast, patients with neither lifestyle-limiting angina nor objective evidence of significant myocardial ischemia do not benefit from the treatment of mild/intermediate coronary lesions, in terms of improved anginal status, quality of life, or freedom from subsequent death or MI (4,7). In particular, stenoses <50% typically do not impede coronary flow reserve (33), and studies have consistently shown that intermediate lesions with fractional flow reserve of either >0.75 or >0.80 can safely have revascularization deferred with similar (DEFER [Deferral Versus Performance of PTCA in Patients Without Documented Ischemia] trial) (8) or even decreased (FAME [Fractional Flow Reserve Versus Angiography for Multivessel Evaluation]) (9) adverse event rates compared with preemptive revascularization. Importantly, these guidelines refer to stenosis severity estimated by QCA rather than visual estimation, which is known to overestimate stenosis severity by 15% to 20% (34).

The present study has several important clinical implications. Routine angiographic follow-up, particularly if cou-

pled with oculostenotic repeat revascularization of intermediate nonischemic lesions, increases health care expenses without associated improvement in long-term prognosis, compared with clinical follow-up alone in which repeat angiography is reserved to evaluate recurrent symptoms or objective evidence of myocardial ischemia. Moreover, use of routine angiographic follow-up can distort the results of clinical trials, especially when the temptation for oculostenotic reintervention is not well-controlled. Because roughly one-half of patients with angiographic restenosis (defined as >50% DS by QCA) have sufficiently severe restenosis (generally >70% DS by QCA) to cause recurrent ischemia, well-controlled trials generally show a "conversion rate" from binary angiographic restenosis to repeat TLR of approximately 50% (22–24,35,36). By contrast, some trials have reported conversion rates from angiographic restenosis to TLR in excess of 70%, resulting in disparate results of stent performance as reported from either pivotal trials or large registries (22–24,35–38). To avoid misleading results, protocol design should require stenosis >70% by QCA or objective evidence of ischemia as a threshold for performing repeat revascularization (or considering a repeat revascularization to be ischemia-driven).

This analysis has several important limitations. First, it is a post hoc analysis rather than a randomized controlled trial comparing routine angiographic versus clinical-only follow-up. Second, the 3 pooled trials differed slightly in their inclusion/exclusion criteria, and the results from the TAXUS Express and Liberté stents in WH lesions were pooled (39). Third, given that there was systematically greater use of routine angiographic follow-up in the anatomically more complex TAXUS V study, it was necessary to perform a secondary analysis selecting propensity-matched angiographic and clinical follow-up groups, which might have failed to balance other unmeasured variables. Fourth, the statistical power was not sufficient to detect small differences between the angiographic and clinical-only follow-up groups for clinical end points other than TLR. Fifth, untreated patients with intermediate lesions at 9 months were assumed to be ischemia-free, and no CEC adjudication for angina status was performed in patients who had not sustained a clinical event. Therefore, some patients who exhibited ischemia at the time of the 9-month angiogram but were felt to be unsuitable for revascularization might have been included in the group of untreated patients. Finally, no long-term anginal status or quality of life data are available in these studies. Given these limitations, this analysis should be considered hypothesis-generating rather than a definitive analysis of the value of routine follow-up angiography after DES implantation, but it certainly does not suggest any clinical benefit of routine angiographic follow-up in clinical practice.

Conclusions

The practice of routine angiographic follow-up after DES implantation leads to increased rates of repeat revascularization via the oculostenotic treatment of mild to intermediate lesions. There is no evidence that either routine angiographic follow-up per se or the oculostenotic treatment of such intermediate lesions provides any net clinical benefit through 5 years of follow-up as compared with clinical follow-up only where angiography is reserved for recurrent symptoms or objective evidence of ischemia. Moreover, if angiographic follow-up is performed, leaving asymptomatic and nonischemia-producing intermediate lesions untreated poses no increased risk of death or MI and can avoid the majority of repeat revascularizations.

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Key Words: drug-eluting stent ■ intermediate lesions ■ meta-analysis ■ oculostenotic reflex.